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METABOLIC DISEASE

Leptin sensitizer reverses obesity

Leptin is an adipocyte-derived hormone that acts on the central nervous system (CNS) to regulate appetite and body weight. Despite high levels of circulating leptin, obese patients develop central leptin resistance, and leptin therapy is therefore ineffective. Now, writing in *Nature Medicine*, Ozcan and colleagues report that the plant-derived compound, withaferin A, restores leptin sensitivity, promotes weight loss and improves glucose metabolism in diet-induced obese (DIO) mice.

Increased endoplasmic reticulum (ER) stress in hypothalamic neurons has a key role in the development of leptin resistance and obesity. Previously, the authors searched the Broad Institute Connectivity Map (CMAP) database for small molecules with gene expression signatures similar to those of models of ER stress and leptin resistance reversal in the mouse liver and hypothalamus. This led to the identification of celastrol as a potent leptin sensitizer. The authors therefore set out to determine whether the gene expression profile of celastrol itself could be used to identify novel leptin sensitizers.

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To do this, they analysed microarray data from mouse embryonic fibroblasts treated with vehicle or celastrol, and created a gene expression signature comprising the 20 most upregulated and the 20 most downregulated genes by celastrol. Querying the CMAP database with this signature identified withaferin A (a steroidal lactone derived from the medicinal plant *Withania somnifera*) as one of the top-ranking chemical compounds, exhibiting a gene expression profile highly similar to that of celastrol. Analysis of microarray data from celastrol- and withaferin-A-treated DIO mice showed a high degree of similarity between the hypothalamic gene expression profiles.

Treatment of leptin-resistant DIO mice with withaferin A for 21 days reduced body weight by 23%, decreased food intake by 62%, significantly lowered circulating leptin concentrations, lowered fat mass by 35% and reduced hepatic steatosis compared to vehicle-treated DIO mice. The withaferin-A-mediated reduction in food intake and weight loss gradually normalized as leptin levels decreased.

Furthermore, although leptin administration had no beneficial effects in DIO mice, pretreatment of these mice with withaferin A sensitized them to leptin, resulting in a greater decrease in body weight and food consumption compared to mice receiving withaferin A treatment alone. By contrast, withaferin A had only a minimal effect on these parameters in *ob*/*ob* or *db*/*db* mice, which lack leptin or the leptin receptor, respectively.

Analysis of signal transducer and activator of transcription 3 (STAT3) phosphorylation (a downstream component of the leptin signalling pathway) revealed that withaferin A, similarly to celastrol, sensitizes leptin receptor signalling substantially in the ventromedial hypothalamus and dorsomedial hypothalamus of DIO mice. As expected, withaferin A was found to alleviate ER stress in the hypothalamus of DIO mice.

Withaferin A treatment also improved glucose homeostasis in DIO mice. Surprisingly, and in contrast to celastrol, similar beneficial effects were observed in *ob*/*ob* and *db*/*db* mice, suggesting that withaferin A has antidiabetic effects that are independent of leptin signalling.

In summary, this study identifies withaferin A as a potential novel treatment for obesity and associated metabolic disease. Furthermore, these findings demonstrate the use of gene expression profiling as a promising drug discovery approach.

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